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PTO/SB/16 (10-01)

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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

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INVENTOR(S)

Given Name (first and middle [if any])	Family Name or Surname	Residence (City and either State or Foreign Country)
Thomas J.	Smith	Weston, MA

☐ Additional inventors are being named on the _______ separately numbered sheets attached hereto

TITLE OF THE INVENTION (500 characters max)

Large Crystalline Formulations for Sustained Release Delivery of Antibiotics for the Prohpylaxis or Treatment of Anthrax

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ENCLOSED APPLICATION PARTS (check all that apply)

☑ Specification Number of Pages 17

☐ Drawing(s) Number of Sheets

☐ Application Data Sheet. See 37 CFR 1.76

☐ CD(s), Number

☐ Other (specify)

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT

☑ Applicant claims small entity status. See 37 CFR 1.27.

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Respectfully submitted,

SIGNATURE Lisa M. Portscher

Date 12/20/02

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REGISTRATION NO. (if appropriate) N/A

Docket Number: TJS-006

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TOTAL AMOUNT OF PAYMENT	($) 80.00

Complete if Known	
Application Number	Unknown
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FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1001	740	2001	370	Utility filing fee	
1002	330	2002	165	Design filing fee	
1003	510	2003	255	Plant filing fee	
1004	740	2004	370	Reissue filing fee	
1005	160	2005	80	Provisional filing fee	80.00

SUBTOTAL (1) ($) 80.00

2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE

			Extra Claims		Fee from below		Fee Paid
Total Claims		-20** =		X		=	
Independent Claims		- 3** =		X		=	
Multiple Dependent					0	=	0

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
1202	18	2202	9	Claims in excess of 20
1201	84	2201	42	Independent claims in excess of 3
1203	280	2203	140	Multiple dependent claim, if not paid
1204	84	2204	42	** Reissue independent claims over original patent
1205	18	2205	9	** Reissue claims in excess of 20 and over original patent

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FEE CALCULATION (continued)

3. ADDITIONAL FEES

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1051	130	2051	65	Surcharge - late filing fee or oath	
1052	50	2052	25	Surcharge - late provisional filing fee or cover sheet	
1053	130	1053	130	Non-English specification	
1812	2,520	1812	2,520	For filing a request for *ex parte* reexamination	
1804	920*	1804	920*	Requesting publication of SIR prior to Examiner action	
1805	1,840*	1805	1,840*	Requesting publication of SIR after Examiner action	
1251	110	2251	55	Extension for reply within first month	
1252	400	2252	200	Extension for reply within second month	
1253	920	2253	460	Extension for reply within third month	
1254	1,440	2254	720	Extension for reply within fourth month	
1255	1,960	2255	980	Extension for reply within fifth month	
1401	320	2401	160	Notice of Appeal	
1402	320	2402	160	Filing a brief in support of an appeal	
1403	280	2403	140	Request for oral hearing	
1451	1,510	1451	1,510	Petition to institute a public use proceeding	
1452	110	2452	55	Petition to revive - unavoidable	
1453	1,280	2453	640	Petition to revive - unintentional	
1501	1,280	2501	640	Utility issue fee (or reissue)	
1502	460	2502	230	Design issue fee	
1503	620	2503	310	Plant issue fee	
1460	130	1460	130	Petitions to the Commissioner	
1807	50	1807	50	Processing fee under 37 CFR 1.17(q)	
1806	180	1806	180	Submission of Information Disclosure Stmt	
8021	40	8021	40	Recording each patent assignment per property (times number of properties)	
1809	740	2809	370	Filing a submission after final rejection (37 CFR 1.129(a))	
1810	740	2810	370	For each additional invention to be examined (37 CFR 1.129(b))	
1801	740	2801	370	Request for Continued Examination (RCE)	
1802	900	1802	900	Request for expedited examination of a design application	

Other fee (specify) ____________

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SUBMITTED BY				(Complete (if applicable))	
Name (Print/Type)	Lisa M. Portscher	Registration No. (Attorney/Agent)	N/A	Telephone	617-361-5434
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Express Mail Label No.EU792050061
Atty. Docket No.TJS-006

LARGE CRYSTALLINE FORMULATIONS FOR SUSTAINED RELEASE DELIVERY OF ANTIBIOTICS FOR THE PROHPYLAXIS OR TREATMENT OF ANTHRAX.

BACKGROUND OF THE INVENTION

Field of the Invention.

This invention relates to the field of pharmaceutical sciences, and particularly to the formulation of sustained-release drug delivery systems for antibiotics useful in the prophylaxis or treatment of anthrax.

Description of the Related Art.

1. Anthrax

The 5 deaths from anthrax in the United States in 2001 brought bioterrorism and its potential to sharp focus; thousands of people received prophylactic antibiotics. Although there is a vaccine for anthrax its ability to prevent the disease is sufficiently weak that prophylactic antibiotics are recommended to anyone suspected of exposure. In a study in primates, monkeys that were exposed to inhalational anthrax either with or without vaccination uniformly died. When the monkeys were treated with antibiotics of the penicillin, tetracycline or fluoroquinolone classes however their survival rate was high (*Postexposure prophylaxis against experimental inhalation anthrax*. J Infect Dis 1993 May; 167(5):1239-43. Friedlander AM, Welkos SL, Pitt ML, Ezzell JW, Worsham PL, Rose KJ, Ivins BE, Lowe JR, Howe GB, Mikesell P, et al.)

Bacillus anthracis is an aerobic, gram-positive, sporulating bacillus measuring approximately 1-3μ in size. The spores are inhaled into the lungs, where alveolar macrophages ingest the organisms and initiate the pathological process The minimum infecting dose is not known but 8000–40,000 spores is the LD_{50} in experimental infection of nonhuman primates.

The most characteristic pathologic features are hemorrhagic thoracic lymphadenitis and hemorrhagic mediastinitis. Focal hemorrhagic, necrotizing pneumonia

hemorrhagic meningitis, submucosal intestinal hemorrhages and large hemorrhagic pleural effusions are common. The incubation period is approximately 4–6 days.

Most hosts are previously healthy adults. The disease tends to be fulminant, and it tends to occur in 2 stages that may merge imperceptibly. The first stage is characterized by nonspecific flu-like symptoms. The second stage is characterized by dyspnea, fever, and shock. The mean duration of the first stage is 3–4 days, and the median duration of the second stage before death is 1 day.

Recommendations for antibiotic treatment of inhalational anthrax include use of either ciprofloxacin, procaine penicillin or doxycycline. These agents have been approved by the US Food and Drug Administration (FDA) for the treatment of anthrax, and they have been shown to be effective in preventing infection in monkey models when given after aerosol challenge. The CDC recommendation is for combination therapy, which includes one of these antibiotics plus 1–2 additional antibiotics that are known to be active in vitro against B. anthracis. These include erythromycin, azithromycin, clarithromycin, clindamycin, rifampin, and vancomycin. Antibiotic selection for any future episodes should be dictated by the results of in vitro susceptibility testing of the implicated strain. (Bartlett JG, Inglesby TV, and Borio L. Management of Anthrax. Clinical Infectious Diseases. 2002; 35:851-85)

It is estimated that only 45 % of patients actually adhere to treatment regiments for prophylaxsis after anthrax exposure (Adherence to Antimicrobial Inhalational Anthrax Prophylaxis among Postal Workers, Jefferds MD, Laserson K, et al. Emerging Infectious Diseases. Washington, D.C., 2001). Therefore any therapeutic modality which could increase adherence to therapy could have a therapeutic utility. It is well recognized in other treatment regimens such as the outpatient treatment of schizophrenia or in birth control programs that sustained release injectable therapy increases adherence to therapy. It is thus an object of this invention to produce a sustained release injectable therapy for the prophylaxis or treatment of anthrax.

2. <u>Oral and Parenteral Formulations</u>

Antibiotics used for the prophylaxis and treatment of anthrax are currently formulated for oral ingestion or parenteral injection. Therefore it is essential that the drugs dissolve into the gastro-intestinal or parenteral fluids in order to be absorbed into

the body. For this reason, fluoroquinolone antibiotics have been formulated as small particles that either have been mixed with binding agents and pressed into pills or tablets for oral administration, or have been dissolved in physiologically acceptable aqueous solvents for parenteral administration.

According to the Noyes Whitney Equation:

$$dc/dt = kS\,(Cs - Ct) \qquad (1)$$

where *dc/dt* is the rate of dissolution, *k* is the dissolution rate constant, *S* is the surface area of the dissolving solid, *Cs* is the saturation concentration of drug in the diffusion layer and *Ct* is the concentration of drug in the dissolution media (or the bulk).

Of the variables in equation 1, only the surface area, *S*, is easily manipulated and, therefore, it is *S* which ultimately determines the rate of dissolution and drug delivery. In the prior art, fluoroquinolone antibiotics have been formulated as small particles by milling in order to increase the surface area-to-volume ratio and therefore aid in rapid dissolution.

Furthermore, many drugs can be formulated as one of several polymorphs in order to alter their stability and dissolution properties. Polymorphism is the chemical characteristic of solid substances that can exist in one or more crystalline and/or amorphous forms. The different polymorphs are usually designated by Roman numerals, with the most stable polymorph under ambient conditions being designated as Form I. In order to increase their dissolution, some drugs are formulated as less stable polymorphs or as amorphous forms.

3. Sustained Release Formulations

In certain situations, it is desired that a fluoroquinolone antibiotic be administered in a sustained release formulation, typically with the objectives of achieving a nearly constant, or zero order, release rate over a significant period of time and reducing the problem of non-compliance or non-adherence to therapy. Most sustained release systems employ a finely milled or micronized preparation of the active pharmaceutical ingredient as a starting point in the formulations. The release of the active pharmaceutical ingredient into the body is then controlled using matrices, membranes or other inactive ingredients or devices. Examples of methods and devices known in the art for sustained

release formulations include liposomes, bioerodable matrices (e.g., PLA/PGLA matrices), drug-permeable implants (e.g., U.S. Pat. No. 3,993,073 to Zaffaroni), implants with drug-permeable and drug-impermeable membranes (e.g., U.S. Pat. No. 5,378,475 to Smith et al.), and osmotic drug delivery systems (e.g., U.S. Pat. No. 4,439,196 to Higuchi).

The production and use of pharmaceutical preparations including larger drug particles to sustain delivery have been described in the art for certain antibiotics, insulin and steroids (see, e.g., Ansel, Allen and Popovich, eds., Pharmaceutical Dosage Forms and Drug Delivery Systems, 7th Edition, Lippincott Williams & Wilkins, Philadelphia, PA, 1999; Gennaro ed., Remington: The Science and Practice of Pharmacy, 19th Edition, Lippincott Williams & Wilkins, Philadelphia, PA, 1995), but, apart from procaine penicillin, the use of this technique has not been applied to the delivery of drugs for the treatment of anthrax .

For example, suspensions of crystals of benzathine and procaine penicillin are useful in the treatment of rheumatic fever and other infections. Typically, therapeutic levels of these antibiotics can be sustained for 14-28 days after a single IM injection (Cadorniga et al. (1991), *Eur. J. Drug Metab. Pharmacokinet.* 3:379-84; Kaplan et al. (1989), *J. Pediatr.* 115(1):146-50; U.S. Pat. No. 2,627,491; U.S. Pat. No. 2,515,898).

Similarly, suspensions of crystals of zinc insulins have slow release properties that depend on crystal size (Nichols (2000), in Remington: The Science and Practice of Pharmacy, Gennaro, ed., Lippincott Williams & Wilkins: Philadelphia, PA. p. 1371). The principal determinant of sustained antiglycemic action in these slow-release or "lente" insulin preparations is the dissolution of the insulin crystals.

Sustained release suspensions of corticosteroids for local delivery (intralesional, intra-articular) or systemic delivery achieve their duration of action due to slow dissolution of crystals of insoluble salts (Mollmann et al. (1977), *Fortschr. Med.* 95(14): 972-8).

There remains a need, however, for new and improved methods and products for the sustained release delivery of anti-anthrax antibiotics.

SUMMARY OF THE INVENTION

The present invention is generally directed to the production and use of pharmaceutical preparations including large and/or shape-controlled coated or uncoated crystalline formulations for the purpose of sustained-release delivery of anti-anthrax antibiotics. The invention depends, in part, upon the recognition that, if a larger crystal of a drug is introduced, there will be a sustained release effect due to the decreased surface area-to-volume ratio of the larger particles. In addition, if the particle is formulated to be substantially flat, then the kinetics of drug release can be made to approach zero order or linear delivery. Moreover, formulation using the most stable polymorph (Form I) will aid in sustaining release because of decreased solubility from the surface, and will also increase the chemical stability of the active pharmaceutical ingredient. Furthermore, the coating of the particle with a semi-permeable membrane can cause the delivery rate to be predicated by the difference in the concentration of drug in solution between the inside and outside of the coating. The chemical potential difference between the inside and outside will be constant as long as the solution is saturated inside and at a "sink" concentration outside. In the present invention, such conditions will apply for the majority of the drug delivery time period, therefore causing sustained pseudo-zero order delivery.

In some embodiments of the invention, the crystals have at least one linear dimension greater than 50μm, greater than 100μm, greater than 500μm, or greater than 1mm. In some embodiments in which the formulations are heterogeneous with respect to crystal size, at least 70%, 80%, 90% or 95% of the crystals have at least one linear dimension greater than 50μm, greater than 100μm, greater than 500μm, or greater than 1mm.

In some embodiments, the formulations are produced as bodies which are relatively thin in one dimension relative to perpendicular dimensions, such as substantially flat or disc-shaped bodies.

In some embodiments, the active pharmaceutical ingredient is crystallized in a stable crystalline form, or the most stable of multiple crystalline forms.

In some embodiments, the pharmaceutical preparation of the invention is a surgically implantable or injectable (via a needle/trochar) implant.

In some embodiments, the pharmaceutical preparation of the invention is an injectable suspension.

In some embodiments, the crystals are uncoated.

In some embodiments, the crystals are coated with a biodegradable semi-permeable polymer coating. In specific embodiments, the coating can be PLA; PLGA; a polyorthoester; or a polyanhydride.

In some embodiments, the crystals are coated with a biocompatible semi-permeable polymer coating. In specific embodiments, the coating can be PVA; EVA; or silicone.

In another aspect, the invention provides methods for treating a mammal suffering from or at risk of a condition for which administration of a anti-anthrax antibiotic is indicated. The methods involve administering a pharmaceutical preparation of the invention to the mammal such that an effective amount of the active pharmaceutical ingredient is provided over a sustained period of time.

In another aspect, the invention provides a pharmaceutical preparation and kits comprising large crystalline particles. In some embodiments, the large crystalline particles are in a dry form that can be suspended in a separately provided diluent prior to use. In some embodiments, a kit is provided containing separate containers of the large crystalline particles in a dry form and a diluent for forming the suspension prior to use. In other embodiments, a multi-chambered product is be provided in which the large crystalline particles are contained in one chamber in a dry form and a diluent is contained in another chamber, such that a suspension is formed when the wall separating the chambers is ruptured and the particles and diluent are mixed.

DETAILED DESCRIPTION

General Considerations.

The present invention is generally directed to the production and use of pharmaceutical preparations including large crystalline formulations for the purpose of sustained-release delivery of anti-anthrax antibiotics. In contrast to the teachings of the prior art, the present invention is dependent, in part, upon the discovery that large crystalline formulations of these active pharmaceutical ingredients, employing crystals

having linear dimensions exceeding 50μm, 100μm, 500μm, or even 1mm, are useful for sustained-release drug delivery. Moreover, it has been discovered that such large crystalline formulations can be produced in flattened shapes (i.e., shapes in which the body is substantially smaller in one linear dimension relative to perpendicular dimensions) which dissolve with pseudo-zero order kinetics. Furthermore, the coating of such crystals can enhance the linearity of release. Some active pharmaceutical ingredients can exist in multiple crystalline forms. For such active ingredients, it has been discovered that the stable or most stable form is the most useful for sustained release drug delivery.

Definitions.

All technical and scientific terms used herein, unless otherwise defined below, are intended to have the same meaning as commonly understood by one of ordinary skill in the art; references to techniques employed herein are intended to refer to the techniques as commonly understood in the art, including variations on those techniques or substitutions of equivalent techniques which would be apparent to one of skill in the art. In order to more clearly and concisely describe the subject matter which is the invention, the following definitions are provided for certain terms which are used in the specification.

The term "pharmaceutically acceptable carrier" as used herein means a material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material, involved in carrying or transporting the active pharmaceutical ingredients from one organ, or portion of the body, to another organ, or portion of the body. Each carrier must be "pharmaceutically acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient (i.e., suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problems or complications, commensurate with a reasonable benefit/risk ratio).

As used herein, the term "effective amount" of an active pharmaceutical ingredient means the total amount of the active pharmaceutical ingredient in a composition that is sufficient to cause a statistically significant change of a detectable

biochemical or phenotypic characteristic. When applied to an individual active pharmaceutical ingredient, administered alone, the term refers to that ingredient alone. When applied to a combination, the term refers to combined amounts of the active pharmaceutical ingredients that result in the effect, whether administered in combination, serially or simultaneously.

As used herein, the term "substantially pure" means a preparation which contains at least 60% (by dry weight) of the active pharmaceutical ingredient of interest, exclusive of the weight of other intentionally included compounds. In certain embodiments, the preparation is at least 75%, at least 90%, or at least 99% the active pharmaceutical ingredient of interest by dry weight, exclusive of the weight of other intentionally included compounds. Purity can be measured by any appropriate method, e.g., column chromatography, gel electrophoresis, amino acid compositional analysis or HPLC analysis. If a preparation intentionally includes two or more different active pharmaceutical ingredients of the invention, a "substantially pure" preparation means a preparation in which the total dry weight of the active pharmaceutical ingredients of the invention is at least 60% of the total dry weight, exclusive of the weight of other intentionally included compounds. For preparations containing two or more active pharmaceutical ingredients of the invention, the total weight of the active pharmaceutical ingredients of the invention should be at least 75%, at least 90%, or at least 99%, of the total dry weight of the preparation, exclusive of the weight of other intentionally included compounds. Thus, if the active pharmaceutical ingredients of the invention are mixed with one or more other compounds (e.g., diluents, stabilizers, detergents, excipients, salts, sugars, lipids) for purposes of administration, stability, storage, and the like, the weight of such other compounds is ignored in the calculation of the purity of the preparation.

As used herein, the term "mammalian subject" means any member of the class Mammalia including, without limitation, humans and nonhuman primates such as chimpanzees and other apes and monkey species; farm animals such as cattle, sheep, pigs, goats and horses; domestic mammals such as dogs and cats; laboratory animals including rodents such as mice, rats and guinea pigs, and the like. The term does not denote a particular age or sex. Thus, adult and newborn subjects, as well as fetuses, whether male or female, are intended to be covered.

As used herein, the terms "modulate" or "affect" mean to either increase or decrease. As used herein, the terms "increase" and "decrease" mean, respectively, statistically significantly increase (*i.e.*, $p < 0.5$) and statistically significantly decrease (*i.e.*, $p < 0.5$).

As used herein, the recitation of a numerical range for a variable is intended to convey that the invention may be practiced with the variable equal to any of the values within that range. Thus, for a variable which is inherently discrete, the variable can equal each integer value of the numerical range, including the end-points of the range. Similarly, for a variable which is inherently continuous, the variable can equal each real value of the numerical range, including the end-points of the range. As an example, a variable which is described as having values between 0 and 2, can be 0, 1 or 2 for variables which are inherently discrete, and can be 0.0, 0.1, 0.01, 0.001, or any other real value ≤ 2 for variables which are inherently continuous.

As used herein, unless specifically indicated otherwise, the word "or" is used in the "inclusive" sense of "and/or" and not the "exclusive" sense of "either/or."

<u>Crystal Size.</u>

In one aspect, the invention provides pharmaceutical formulations in which the active pharmaceutical ingredient is in the form of large crystals. This distinguishes the formulations of the invention from prior art formulations in which active ingredients are machined or milled to produce small or micronized crystals of the drug, which then must be combined with matrices, semi-permeable membranes, pumps or other inactive ingredients or devices in order to achieve the effect of sustained release delivery.

In some embodiments, the crystals have at least one linear dimension greater than 50μm, greater than 100μm, greater than 500μm, or greater than 1mm. In some embodiments in which the formulations are heterogeneous with respect to crystal size, at least 70%, 80, 90% or 95% of the crystals have at least one linear dimension greater than 50μm, greater than 100μm, greater than 500μm, or greater than 1mm.

Body Shape.

The shape of a solid formulation, including implants or solid bodies that may be present in a liquid suspension, can be described by reference to three perpendicular or orthogonal axes. In some embodiments, the formulations are produced as bodies which are substantially smaller in one dimension relative to perpendicular dimensions, such as substantially flat or disc-shaped bodies. Such bodies will present a more constant surface area over time during dissolution. Because dissolution occurs at the surface of the body, such relatively constant surface areas are useful to approximate or achieve pseudo-zero order kinetics of delivery.

Crystal Form.

Polymorphism is the chemical characteristic of solid substances that can exist in one or more crystalline and/or amorphous forms. The different polymorphs are usually designated by Roman numerals, with the most stable polymorph under ambient conditions being designated as Form I.

In some embodiments, the active pharmaceutical ingredient is crystallized in a stable crystalline form, or the most stable of multiple crystalline forms (e.g., Form I). Because this crystalline form tends to be the least soluble in water, it has been avoided in the prior art. However, it has been discovered that utilizing the most stable polymorph can significantly enhance the ability to achieve sustained release rates.

Active Pharmaceutical Ingredients.

Active pharmaceutical ingredients which may be formulated according to the invention include any anti-anthrax antibiotic drug which may be crystallized according to the invention. Non-limiting examples of anti-anthrax antibiotics include norfloxacin, ciprofloxacin, ofoxacin, sparfloxacin, lomefloxacin, fleroxacin, perfloxacin, levofloxacin, trovafloxacin, gatifloxacin, moxifloxacin, tetracycline, chlortetracycline, oxytetracycline, demeclocycline, methacycline, doxycycline, minocycline, clindamycin, erythromycin, clarithromycin and azithromycin, gentamicin, tobramycin, amikacin, netilimicin, neomycin, kanamycin and streptomycin, penicillin, chlorpenicillin, oxypenicillin, methicillin, nafcillin, oxacillin, cloxacillin, dicloxacillin, ampicillin, amoxicillin,

bacampicillin ; carbenicillin, carbenicillin indanyl, ticarcillin, mezlocillin and piperacillin ; and the like and/or pharmaceutically acceptable salts thereof.

Production of Large Crystalline Formulations.

The large crystalline formulations of the invention, although not produced in the prior art, can be produced by methods well known in the art. The active pharmaceutical ingredients in the formulations can be any anti-anthrax antibiotic for which the large crystalline formulations of the invention can be produced.

1. Solvation Crystallization.

A substantially pure pharmaceutical preparation of the anti-anthrax antibiotic drug is synthesized, isolated or otherwise obtained. The purity is tested to ensure suitability for use in a pharmaceutical preparation.

The active pharmaceutical ingredient is dissolved in an appropriate volatile solvent to form a solution. The solution is then dispensed into properly shaped drying areas, such as flat-bottomed wells or flat or dimpled surfaces. The solvent is then allowed to evaporate at an appropriate rate (e.g., controlling the rate by controlling the temperature and/or the humidity and/or the partial pressure of the solvent or other gases in the ambient atmosphere) to obtain crystals of the desired size.

Alternatively the solution of active pharmaceutical ingredient in solvate is sprayed onto a cooling slab surface. A disc is formed by evaporation of the solvent and the disc parameters (e.g., size, shape, weight) are adjusted by adjusting the parameters of the spraying step (e.g., volume of drops, concentration, ambient pressure and temperature, slab temperature, velocity of spray, nozzle size, etc.).

The resultant crystals are sorted by size and/or subjected to mechanical forces to modify the size or shape of the crystalline bodies. For example, the bodies can be passed through sieves to isolate bodies within desired size ranges, and can be ground, lathed, milled, cut (e.g., with a laser), etc., to reduce the size of alter the shape of the bodies.

2. <u>Melting and Recrystallization</u>.

A substantially pure pharmaceutical preparation of the anti-anthrax antibiotic drug is synthesized, isolated or otherwise obtained. The purity is tested to ensure suitability for use in a pharmaceutical preparation.

The melting point of the active pharmaceutical ingredient is determined by standard methods (e.g., visual inspection while slowly increasing or decreasing ambient temperature and/or by reference to the literature). For each active pharmaceutical ingredient, the optimum melting process is that which melts the drug completely while minimizing molecular breakdown. This optimum process can be determined for each active pharmaceutical ingredient by one skilled in the art through the process of varying key parameters in the melting process (e.g., rate, intensity, agitation or mixing, etc.). The results of the process can be assessed by determining the purity of the resulting melted form (i.e., lack of molecular breakdown) through HPLC or NMR analysis. After melting, the active pharmaceutical ingredient is cooled, actively or passively, so as to promote the formation of large crystals of the desired crystalline form (e.g., Form I). Optimum cooling parameters and process (e.g., mixing, rate of cooling, final temperature, cooling substrate or surface characteristics, etc.) can be determined by varying these parameters experimentally and characterizing the resultant crystals in terms of size, shape and polymorph state.

The resultant crystals can then be sorted by size and/or subjected to mechanical forces to modify the size or shape of the crystalline bodies. For example, the bodies can be passed through sieves to isolate bodies within desired size ranges, and can be ground, lathed, milled, cut (e.g., with a laser), etc., to reduce the size or alter the shape of the bodies.

3. <u>Seed Crystallization</u>.

A substantially pure pharmaceutical preparation of the anti-anthrax antibiotic is synthesized, isolated or otherwise obtained. The purity is tested to ensure suitability for use in a pharmaceutical preparation.

The active pharmaceutical ingredient is dissolved in an appropriate solvent to achieve a saturated solution. The saturated solution is then seeded with a crystal of the

active pharmaceutical ingredient to initiate crystal formation from the saturated solution. The crystals are then harvested (e.g., by straining from solution and drying, or by evaporating the solvent).

The resultant crystals can then be sorted by size and/or subjected to mechanical forces to modify the size or shape of the crystalline bodies. For example, the bodies can be passed through sieves to isolate bodies within desired size ranges, and can be ground, lathed, milled, cut (e.g., with a laser), etc., to reduce the size of alter the shape of the bodies.

4. Pressure.

A substantially pure pharmaceutical preparation of the anti-anthrax antibiotic is synthesized, isolated or otherwise obtained. The purity is tested to ensure suitability for use in a pharmaceutical preparation.

The active pharmaceutical ingredient in powder form is compressed under high pressure (e.g., for 10 to 100 M tons per cm^2; 25 to 50 M tons per cm^2) for a time sufficient for a glass transformation to take place.

The resultant discs can then be sorted by size and/or subjected to mechanical forces to modify the size or shape of the crystalline bodies. For example, the bodies can be passed through sieves to isolate bodies within desired size ranges, and can be ground, lathed, milled, cut (e.g., with a laser), etc., to reduce the size of alter the shape of the bodies.

Coatings.

Standard coating techniques well known in the art can be used to coat the large crystals. Examples include dipping, pan coating and spray coating. Care must be taken that the active pharmaceutical ingredient is not soluble in the solvent used in the polymeric coating. As discussed below, the coating can be a biodegradable polymer, a biocompatible polymer, or a biodegradable biocompatible polymer.

Biodegradable Polymers.

In some of the implementations of this invention, the large crystalline particles or implants are coated with biodegradable polymers. These polymers are well known in the art and examples include: naturally occurring polymers such as sugar phosphates, which are known to be biodegradable, and synthetic polymers such as polylactides and polyglycolic acids, which are also biodegradable. Lactic acid copolymers offer a degree of flexibility in choosing the life of a polymer matrix, because the half-life can be controlled by varying the amount and type of co-monomer used. Examples of suitable copolymers are glycolide, β-propiolactone, tetramethylglycolide, β-butyrolactone, tetramethylglycolide, β-butyrolactone, γ-butyrolactone, pivalolactone, intramolecular cyclic esters of α-hydroxybuteric acid, α-hydroxy, isovaleric acid, α-hydroxycaproic acid, α-hydroxy ethylbuteric acid, α-hydroxy isocaproic, α-hydroxy β-methyl valeric acid, α-hydroxy heptonic acid, α-hydroxy octanic acid, α-hydroxy deccanoic acid, α-hydroxy myristic acid, α-hydroxy stearic acid, α-hydroxy ligocenic acid, and β-phenol lactic acid. As also known in the art, polyglycolic acids can provide excellent biodegradable properties.

Biocompatible Polymers.

In some of the implementations of this invention, the large crystalline particles or implants are coated with biocompatible polymers. These polymers are well known in the art and examples include: acyl substituted cellulose acetates and alkyl derivatives thereof, partially and completely hydrolyzed alkylene-vinyl acetate copolymers; unplasticized polyvinyl chloride; cross-linked homo- and copolymers of polyvinyl acetate; cross-linked polyesters of acrylic and methacrylate; polyvinyl alkyl ethers; polyvinyl fluoride; silicone; polycarbonate; polyurethane; polyamide; polysulphones; styrene acrylonitrile copolymers; cross-linked poly(ethylene oxide); poly(alkylenes); poly(vinyl imidazole); poly(esters); poly(ethylene terephthalate); and chlorosulphonated polyolefins.

Dosage Forms.

In another aspect, the invention provides pharmaceutical preparations comprising one or more of the anti-anthrax antibiotics described above, formulated together with one

or more pharmaceutically acceptable carriers (additives) and/or diluents. As described in detail herein, the pharmaceutical compositions of the invention are specially formulated for administration in the form of large crystalline particles in suspension or in the form of implants. These formulations are administered by parenteral administration, for example, by subcutaneous or intramuscular injection for suspensions, or by subcutaneous or intramuscular implantation for implants. Implants or suspensions may be designed for local, or targeted, delivery or for systemic delivery of the drug.

Because of the potential for embolic sequelae, intravenous or intra-arterial injections may not be appropriate, and subcutaneous (SC) or intramuscular (IM) injections may be safer. An injection volume of 0.1 to 10 cc, or 1 to 6 cc, can be used for IM injection, and a volume of 0.1 to 2 cc can be used for SC.

In some embodiments of the invention, the crystals of the anti-anthrax antibiotic drug are suspended in a pharmaceutically acceptable carrier which serves as a dispersion medium to form a suspension for injection into a subcutaneous or intramuscular position for sustained pseudo-linear delivery over a period of greater than 1 week, greater than 2 weeks, greater than 4 weeks, or greater than 12 weeks.

Suspensions of large particles will tend to settle more rapidly than suspensions of small particles. Therefore, in some embodiments, a commercial product of the invention can be distributed as large crystalline particles in a dry form that can be suspended in a separately provided diluent prior to use. In other embodiments, a kit is provided containing separate containers of the large crystalline particles in a dry form and a diluent for forming the suspension prior to use. Alternatively, a multi-chambered product can be provided in which the large crystalline particles are contained in one chamber in a dry form and a diluent is contained in another chamber, such that a suspension is formed when the wall separating the chambers is ruptured and the particles and diluent are mixed. In addition to the diluent, appropriate suspending agents and surfactants well known in the art can be included.

When administered in the form of a suspension, a liquid carrier such as water, physiological saline solution, petroleum, oil (e.g., animal, plant or mineral oils, such as cottonseed, groundnut, corn, germ, olive, castor, peanut, mineral, soybean, sesame, or synthetic oils) can be used. The suspension form of the pharmaceutical can further

contain inert diluents commonly used in the art, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, ethyl oleate, benzyl alcohol, benzyl benzoate, glycols (e.g., ethylene glycol, propylene glycol, polyethylene glycol, 1,3-butylene glycol), glycerol, tetrahydrofuryl alcohol, dextrose or other saccharide solutions, and mixtures thereof. Suspensions, in addition to the active compounds, can contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan fatty acid esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof. When administered in suspension form, the pharmaceutical composition can contain about 0.01 to 99% by weight of the crystals, 0.1 to 90% of the crystals, or about 1 to 50% of the crystal.

Pharmaceutically acceptable carriers can include solutions or mixtures of compounds such as sugars, such as lactose, glucose and sucrose; starches, such as corn starch and potato starch; cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; gelatin; oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols, such as propylene glycol; polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; esters, such as ethyl oleate and ethyl laurate; agar; alginic acid; isotonic saline; Ringer's solution; ethyl alcohol; phosphate buffer solutions; and other non-toxic compatible substances routinely employed in pharmaceutical formulations.

In some embodiments of the invention, the crystals of the anti-anthrax antibiotic drug are molded, shaped, compressed or formed into a solid implant for implantation into a subcutaneous or intramuscular position for sustained pseudo linear delivery over a period of greater than 1 week, greater than 2 weeks, greater than 4 weeks, or greater than 12 weeks. Such implants can include (1) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and/or silicic acid; (2) binders, such as, for example, carboxymethylcellulose, hydroxypropylmethyl cellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; or (3) embedding compositions, such as polymeric substances and waxes.

Methods of Treatment.

In another aspect, the invention provides methods for treating a mammal suffering from or at risk of. In general, the methods involve administering a pharmaceutical preparation of the invention to the mammal such that an effective amount of the active pharmaceutical ingredient is provided over a sustained period of time. The mammals can be humans, or can be nonhuman primates such as chimpanzees or other apes or monkey species; farm animals such as cattle, sheep, pigs, goats and horses; domestic mammals such as dogs and cats; laboratory animals including rodents such as mice, rats and guinea pigs, and the like.

The sustained release formulation can be a coated or uncoated large crystal, or a coated or uncoated implant. In those embodiments in which the crystals or implants are coated, the coating can be a biodegradable polymer and/or a biocompatible polymer. In those embodiments in which the formulation includes large crystals, the crystals can be held in a suspension for injection.

In some embodiments, the formulations will be designed to provide sustained pseudo-linear delivery over a period of greater than 1 week, greater than 2 weeks, greater than 4 weeks, or greater than 12 weeks. The amount of the drug and the rate of delivery can be determined by the physician and/or pharmacist and will depend upon such factors as the potency of the active pharmaceutical ingredient, the severity of the condition, and the age, sex and weight of the subject. The rate of drug delivery is determined to provide an effective amount of the active pharmaceutical ingredient over a sustained period of time.

EQUIVALENTS

While this invention has been particularly shown and described with references to certain embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the spirit and scope of the invention. Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described specifically herein. Such equivalents are intended to be encompassed in the scope of the invention.

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